Remarks

Favorable action on the merits is respectfully requested in view of the preceding amendments and the following comments.

The amendment to claim 1 finds clear antecedent support, e.g., in the first complete sentence on page 5 of the specification. The amendments to claim 15 are based on the first paragraph on page 5 and the working examples. The amendment to claim 17 finds clear antecedent support in the working examples wherein the compositions according to the invention are inherently all in suspension form. The amendment to claim 20 is completely editorial in nature. The amendment to claim 21 is inherent in view of the syringeability of the compositions.

Newly presented claims 28 to 34 find clear and complete antecedent support in the same manner as prior claim 22, on which they are based.

Applicants respectfully submit that, to those of at least ordinary skill in the art, it is scientifically clear that the claimed compositions are in the form of suspensions.

In the Advisory Action (Paper No. 11) of August 28, 2003, the Examiner states:

> U.S. Patent 5,520,927 teaches that the compositions of the invention comprise lecithin (*See* Example 1), PEG-lanolin (*See* Example 14) or Arlacel 165 (*See* Example 15), and said compounds are lubricants.

Issue is respectfully taken with this unsupported and unsupportable allegation insofar as its intent relates to "a pharmaceutically acceptable lubricant", as expressly called for by each of Applicants' claims.

According to "Hack's Chemical Dictionary", 4th Edition, page 384 (copy herewith), McGraw-Hill Book Company, 1969, lecithin is:

> Brown wax in animal and vegetable tissues and egg yolk...

Arlacel 165 is glyceryl monostearate, which is defined by the same reference at page 302 (copy herewith) as:

> A hard fat, containing 30-40% of the α isomer, m.54-60 dispersible in water.

The undersigned is advised that PEG-lanolin, a product also known as "Solan", is a solid at room temperature.

As the allegation that the noted substances are "lubricants" appears to be in direct conflict with authoritative definitions thereof insofar as "pharmaceutically acceptable lubricants" are concerned, the entire adverse holding in this case is submitted to be completely overcome. Please note that Arlacel 165 is also in solid state at room temperature and cannot be used as a lubricant. Arlacel 165 and PEG-lanolin are used in making nano particles.

Applicants take issue with the out-of-context interpretation of "a derivative of polyethylene glycol and glycerine". That expression is limited to a lubricant; its further limitation to a product "which can be mixed with the lipid-soluble vitamin makes it clear to any artisan that it is limited to a liquid and thus is readily distinguishable from any product which is a solid at ambient temperature.

The core of the present invention is to provide a somatotropin suspension which can markedly decrease pain and stimulation for an injected region of medicated animals, and be administrated conveniently by reducing the volume of the suspension and improving syringeability by adding the injection-friendly substance called "lubricant" (in this invention) which has no effect on the pharmaceutical and releasing effect of the somatotropin.

By adding the lubricant, the present invention solves the problem of conventional somatotropin suspensions containing vitamin E acetate; the high content of somatotropin in the suspension could not previously be achieved due to the high viscosity of vitamin E acetate.

For example, one formerly had to inject at least 5 ml of suspension to administer 500 mg of somatotropin. But by this invention, one can merely inject less than 2 ml of suspension for that purpose. This means that the total volume of somatotropin suspension can be decreased by more than 60%. And if administered in the same volume, the syringeability, especially the low temperature syringeability, is markedly improved.

There was previously no syringeable somatotropin suspension containing vitamin E with over 10% of somatotropin concentration; and, if prepared, it could not be used for lack of syringeability.

The Advisory Action (Paper No. 11) states:

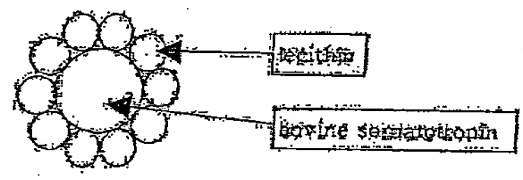
> With regard to the amount of somatropin [somatotropin] claimed in claim 17, the patent teaches that 161.8 mg of mixture contain 100 mg of somatropin [somatotropin] (*See* Example 1), corresponding to an

amount of 61.8% by weight, thus the patent discloses compositions comprising a concentration of somatropin [somatotropin] even higher than the concentration claimed by Applicant.

Example 1 of USP 5,520,927 discloses that the composition (168 mg) contains 100 mg (i.e. 0.1 g) of somatotropin, which was dissolved to 1 ml of tocopheryl acetate (density = 0.9533, "Merck Index", 13th edition, p. 1693, copy herewith). The concentration of somatotropin is not 61.8% by weight, but 8.92% by weight [100 mg somatotropin/(953.3 mg tocopheryl acetate + 168 mg mixture) x 100]. By this reason, there was no syringeable composition with higher somatotropin concentration prior to the present invention.

Lecithin (L-α-lecithin) in Kim's Example 1 is used for emulsifying of the bovine somatotropin. Through the treatment of a microfluidizer and lyophilization, the lecithin takes the shape of liposome (nano particle) as shown in Fig. 1 below (PDA J. Pharm. Sci. Technol., 1999, 53(4) 168-76; 53 (6) 318-23).

Fig. 1



Lecithin particles are attached to the surface of somatotropin and form a shell. As the somatotropin suspension injected into the body cannot easily be activated, lecithin can be used as a releasing agent in Example 1, and thus permits somatotropin activation after the shell (lecithin) is removed.

Accordingly, the method of Kim's Example 1 provides a somatotropin composition with a good releasing effect by using a tocopheryl acetate-dispersed suspension after lyophilization to provide an intact liposome through the microfluidizer after mixing bovine somatotropin and lecithin.

Finally, there is no indication through Kim's whole specification that lecithin is used as a lubricant in Example 1. Those skilled in the art readily recognize that the lecithin is used for making nano-particles by forming a micro emulsion in view of the steps of microfluidization and lyophilization in Example 1.

In this reason, the lecithin, referred to in Kim's Example 1, is not a lubricant.

PEG-lanolin of Example 14 and Arlacel 165 of Example 15 are also used for the formation of somatotropin into liposomes, as mentioned above, and are not used as a lubricant for the same reason.

According to claim 15, this invention is comprised of somatotropin, lipid-soluble vitamins and pharmaceutically acceptable lubricant. Among those, the lubricant corresponds to a solvent/dispersant, and somatotropin and vitamin correspond to solute. Thus, it is obvious for those skilled in the art that the pharmaceutically acceptable lubricant is necessarily in liquid form.

But, as previously noted, PEG-lanolin exists in solid form at room temperature; Arlacel 165 also exists in solid (bead) form at room temperature http://www.uniquema.com/Uniqema_Product (Catalogue/ProdCat/Products.ASP?Region=Americas&MoveTo=227).

Thus, those substances can only be regarded as examples of releasing agents. They cannot be considered as lubricants (in the instantly disclosed and claimed context) to those skilled in the art.

Breitenbach's Example 12 is related to a skin care cream and a moisturizer cream with collagen. His field of invention is totally different from that of the subject invention; his Example 12 is about a formulation for skin, whereas Applicants' claimed invention is directed to syringeable suspensions suitable for administration by injection.

Furthermore, the skin care cream consists of liquid paraffin 24.0g, PEG-9 stearate 5.0g, beeswax 6.0g, cetyl palmitate 2.0g, 1,3-bis-(1-pyrrolidonyl) butane 3.0g and water 60.0g, and the moisturizer cream with collagen consists of PEG-9 stearate 7.0g, 1,3-bis-(1-pyrrolidonyl) butane 1.5g, cetyl alcohol 6.0g, wool wax 3.0g, dimethicone 2.0g, caprylic/capric acid triglyceride 5.0g, sorbitol 3.0g, collagen 5.0g, (-)alpha-bisabolol 0.1g, preservative q.s., perfume oil q.s., and water 67.4g.

Example 12 contains somatotropin not suitable for injection but for a skin formulation. Those skilled in the art, faced with the problem solved by Applicants, would not even consider Breitenbach's disclosure or his reference to PEG-stearate and cetyl palmitate in Example 12.

The PEG-stearate and cetyl palmitate are general ingredients for cosmetic compositions for skin care (http://www.skinbio.com/ingredients.html), and there is no evidence that they are used as a lubricant in injectables.

Applicants' claimed invention is directed to an injectable suspension.

By the claims and the specification, those skilled in the art can easily recognize that this invention is inherently related to suspensions with improved syringeability.

Applicants' claimed invention is directed to a somatotropin suspension with a lipid-soluble vitamin characterized by inclusion of lubricant which facilitates increasing the somatotropin concentration. By including the lubricant, the suspension (without more) can have a high somatotropin content of, e.g., 10 ~ 50% by weight.

Examples 1 to 17 of this invention show a lubricant-containing suspension and a lubricant-free suspension. They are taken to fill in a syringe in the syringeability measuring device (Test Stand Model 2252 and CPU gauge 9500 series, Aikon Engineering, Japan). After loading the suspension in the syringe, the plunger was pushed by 7.8 cm/min and syringeability was measured [kg·force = N{Newton (S. I.)}] by the highest power value.

For instance, in Example 1, the syringeability of the suspension, which is composed of lubricant-free somatotropin 5g (24% by weight) and vitamin E acetate 15g, is 5.24 (kg·f) at room temperature, and 14.76 (kg·f) at low temperature. But the syringeability of the suspensions containing 0.3g, 0.75g, 1.00g, 1.25g and 1.50g of benzyl alcohol as a lubricant are improved by the degree of 11% [(5.24-4.65)/5.24 x 100], 45%, 52%, 59% and 64% at room temperature, and by the degree of 27%, 32%, 36%, 48% and 61% at low temperature.

The syringeability of the suspension, which is composed of lubricant-free somatotropin 2g (10% by weight) and vitamin E acetate 18g, is 3.42 (kg·f) at room temperature and 11.95 (kg·f) at low temperature. The syringeabiltiy of a suspension containing 1.25g of benzyl alcohol as a lubricant is improved by the degree of 47% [(3.42-1.82)/3.42 x 100] at room temperature, and by a degree of 53% at low temperature.

The syringeability of a suspension, which is composed of lubricant-free somatotropin 8g (40% by weight) and vitamin E acetate 12g, is 9.04 (kg·f) at room temperature, and >20 (kg·f) at low temperature, but the syringeability of a suspension containing 1.25g of benzyl alcohol as a lubricant is improved by the degree of 64% [(9.04-3.23)/9.04 x 100] at room temperature, and by a degree of >50% at low temperature.

As shown above, a somatotropin suspension of the claimed invention has incredibly improved syringeability as compared with conventional somatotropin suspension without lubricant. Thus, in case of injection, the injector can easily inject an animal without any additional force. Therefore, pain imparted to injected animals can be relieved. The effect of the suspension is a significant improvement

over corresponding lubricant-free somatotropin suspensions.

With all due respect, the Advisory Action fails to distinguish between "intended use" and "properties". From a standpoint of patent law, a product and all of its properties are inseparable; they are one and the same thing. The patentability of the product does not depend on the similarity of its structure to that of another product but of the similarity of the former product to the latter. There is no basis in law for ignoring any property in making such a comparison. *In re Papesch*, 137 U.S.P.Q. 43 (CCPA 9163).

Syringeability and injectability are clearly properties, which are significantly improved by Applicants' claimed invention. Moreover, there is absolutely no teaching whatsoever in the applied art of the ability to improve such properties by including a pharmaceutically acceptable lubricant in somatotropin injectable compositions. The ability to improve syringeability is neither disclosed nor suggested by any applied art.

Breitenbach relates to a substance, 1,3-bis(N-lactamyl) propane, which is used as a solvent for pharmaceutical and cosmetic agents. The fact that the solvent can dissolve many pharmaceutical and cosmetic materials and 77 kinds of solute, including somatotropin, vitamin E and fat-soluble vitamins, does not in any way even remotely suggest making suspensions more easily syringeable by incorporating a pharmaceutically acceptable lubricant therewith. Were Applicants' lubricant replaced by Breitenbach's solvent, the claimed compositions would lose their extended releasing effect or their durability. There is no equivalency between that solvent and Applicants' lubricant. Moreover, there is no record basis for establishing any equivalency between the two.

There appears to be some confusion in applicable criteria for patentability. Applicants' claims are in "consisting" format. To preclude patentability by prior art, the prior art must either negate novelty (§102) or render obvious (§103) that which is called for by each claim. The references previously applied to Applicants' claims satisfy neither of these requirements. With all due respect, there is no burden on Applicants to show that additional ingredients would be detrimental. In the event that such a position is maintained, Applicants request the citation of clear supporting authority.

The claimed invention is related to a lubricant-containing suspension which makes it possible to have a high content, e.g., 10 ~ 50% by weight, of somatotropin in an easily syringeable product. This has never previously been accomplished.

Having overcome all the outstanding grounds of rejection, the application is now in condition for allowance, and early action toward that end is respectfully solicited.

Respectfully submitted,

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